Clinical Outcomes of Therapeutic Agents That Block the Platelet Glycoprotein IIb/IIIa Integrin in Ischemic Heart Disease

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Background—Several platelet glycoprotein (GP) IIb/IIIa receptor antagonists have been evaluated in clinical trials. We conducted a systematic overview (meta-analysis) to assess the effect of these compounds on death, myocardial infarction (MI), and revascularization.

Methods and Results—ORs were calculated for 16 randomized, controlled trials of GP IIb/IIIa inhibitors. An empirical Bayesian random-effects model combined the outcomes of 32 135 patients. There was a significant mortality reduction by GP IIb/IIIa inhibitors at 48 to 96 hours, with an OR of 0.70 (95% CI, 0.51 to 0.96; *P*<0.03), equivalent to a reduction of 1 death per 1000 patients treated. Mortality benefits at 30 days (OR, 0.87; 95% CI, 0.74 to 1.02; *P*=0.08) and 6 months (OR, 0.97; 95% CI, 0.86 to 1.10; *P*=0.67) were not statistically significant. For the combined end point of death or MI, there was a highly significant (*P*<0.001) benefit for GP IIb/IIIa inhibitors at each time point. The 30-day OR was 0.76 (95% CI, 0.66 to 0.87), or 20 fewer events per 1000 patients treated. For the composite end point of death, MI, or revascularization, there was also a highly significant (*P*<0.001) benefit for GP IIb/IIIa inhibitors. At 30 days, the OR was 0.77 (95% CI, 0.68 to 0.86), or 30 fewer events per 1000 patients treated. The risk differences for death, death or MI, and composite outcomes were similar at 6 months, indicating a sustained absolute improvement. Similar benefit was seen when trials were subgrouped by therapeutic indication (percutaneous intervention versus acute coronary syndromes).

Conclusions—Application of this new therapeutic class to clinical practice promises substantial benefit for both indications. (*Circulation*. 1998;98:2829-2835.)

Key Words: platelet aggregation inhibitors ■ meta-analysis ■ myocardial infarction ■ mortality ■ revascularization

In 1983, Coller and colleagues[1] described an antibody that blocked the platelet glycoprotein (GP) IIb/IIIa receptor. A chimeric monoclonal antibody,[2] abciximab, was later developed for treatment of patients undergoing high-risk percutaneous intervention. Prompted by the benefit of abciximab in a randomized study,[3] multiple peptide and nonpeptide antagonists of the IIb/IIIa receptor have been developed.[4,5] Large clinical trials[6,7] have evaluated these agents for unstable angina, acute myocardial infarction (MI), and percutaneous coronary intervention indications. This article provides a meta-analysis of available studies to evaluate the impact of intravenous GP IIb/IIIa antagonists on clinical outcomes.

Methods

Trial Selection

Randomized, blinded, controlled trials of parenteral GP IIb/IIIa antagonists were identified through a MEDLINE search. Records between 1980 and 1997 were searched for the words "platelet,"

"random$," and ("inhibi$" or "block$"), where $ is a wild card. Published results were included when available. Publicly presented data also represented several recent trials.

Studies were subgrouped on the basis of the indication for GP IIb/IIIa inhibition. Trials of percutaneous coronary intervention (Table 1) included any study in which the intent to perform a percutaneous procedure was an entry criterion.[3,8–16] Acute coronary syndrome trials enrolled patients with symptoms of acute coronary ischemia without ST-segment elevation on the 12-lead ECG (Table 2).[6,7,17–20] The overview analysis evaluated the entire collection of trials as well as each of the subgroups.

Several of these studies had multiple dose arms, and different trials of the same agents used different dosing strategies. To capture all patients exposed to this compound class, our conservative overview included all treatment arms in the analysis. Two trials (PURSUIT, PRISM Plus) had treatment arms that terminated early. Furthermore, the placebo arm event rate increased as the trials progressed. These trials were evaluated using all patients enrolled before the arm was stopped and patients in the remaining treatment arm with contemporaneous controls after the termination of the stopped arm.

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TABLE 1. Percutaneous Intervention Trials

Study	n	Year	Load, μg/kg	Infusion, dose/min	Duration, h	Heparin Regimen	Primary End Point	Indication
Abciximab								
EPIC[3]	2099	1991	250 250	10 μg Placebo	12	B to ACT 300–350 s, then I to PTT 1.5–2.5×control for ≥12 h	30-d death/MI/revasc	High risk for abrupt closure
EPILOG[5]	2792	1995	250	0.125 μg/kg (max 10 μg)	12	(B to ACT 300 s) vs (B to ACT 200 s)	30-d death/MI/urgent revasc	Elective or urgent intervention
Simoons et al[9]	60	1991	250	10 μg	18–24	B+I to PTT 2.0–2.5×control	In-hospital death/MI/recurrent ischemia with urgent revasc	USA at bed rest with medical therapy
CAPTURE[10]	1265	1993	250	10 μg	18–24	I to ACT 300 s or PTT 2.0–2.5×control	30-d death/MI/urgent intervention for recurrent ischemia	Interventions for USA
RAPPORT[11]	483	1997	250	125 μg/kg	12	B to ACT 300–400 s	6-mo death/MI/TVR	Primary PTCA
Eptifibatide								
IMPACT Hi-Lo[12]	73	1993	180 135 90 135	1.0 μg/kg 0.5 μg/kg 0.75 μg/kg 0.75 μg/kg	18–24	B to ACT 300–350 s	In-hospital death/MI/CABG/repeat intervention, or recurrent ischemia	Elective intervention
IMPACT[13]	150	1993	90 90	1.0 μg/kg 1.0 μg/kg	4 12	B to ACT >300 s, then I to PTT 2–3×control	30-d death/MI/urgent revasc	Elective intervention
IMPACT-II[14]	4010	1994	135 135	0.5 0.75	20–24	B to ACT 300–350 s	30-d death/MI/urgent revasc	Any percutaneous intervention
Tirofiban								
Kereiakes et al[15]	93	1995	5 10 10	0.05 μg/kg 0.10 μg/kg 0.15 μg/kg	16–24	B to ACT 300–350 s, then I to PTT 60–80 s	In-hospital death/MI/urgent revasc	High-risk PTCA
RESTORE[16]	2141	1995	10	0.15 μg/kg	36	B to ACT 300–400 s	30-d death/MI/revasc for recurrent ischemia	Intervention within 72 hours of USA or MI

Load indicates loading dose; B, bolus; ACT, activated clotting time; I, infusion; PTT, partial thromboplastin time; TVR, target-vessel revascularization; and USA, unstable angina.

Adjunctive heparin regimens also differed among trials. All percutaneous intervention trials permitted heparin during the procedure to maintain an activated clotting time between 200 and 400 seconds or an activated partial thromboplastin time of 1.5 to 3 times the control value (Table 1). Postprocedure heparin infusions were permitted in 5 of the 10 percutaneous intervention trials. Heparin was given in all acute coronary syndrome trials except for PARAGON A, PRISM, and PRISM Plus, which randomized patients to heparin or placebo (Table 2).

Clinical End Points   ·

Clinical outcomes studied included death, the composite of death or MI, and the composite of death, MI, or revascularization. Each outcome was evaluated at an early time point (between 48 and 96 hours), at 30 days, and at 6 months. For percutaneous intervention trials, the early end point occurred after the end of the study drug infusion. Patients in acute coronary syndrome trials often received drug during this period. Urgent revascularization events were evaluated at the early and 30-day time points, and the occurrence of any revascularization event was assessed at 6 months. The numbers of patients experiencing events at each time point were compiled for treatment and control arms. Although limited numbers of patients were lost to follow-up in several trials, the amount of incomplete data was expected to be equal among randomized arms. The event rates for each arm reflect the number of events observed divided by the number of patients enrolled, according to intention to treat.

Statistical Analysis

ORs summarizing the effectiveness of GP IIb/IIIa inhibitors were calculated by use of Fast*Pro software.[21] These ORs were combined assuming an empirical Bayesian model described by Hedges and Olkin.[22] Risk differences between control and treatment arms were also combined by use of the same model. The empirical Bayesian random-effects model reduces to a fixed-effects model when the studies are homogeneous. The method accommodated heterogeneity by assuming that the true effect differed among studies and therefore must be represented by a distribution of values instead of a single value. The result was a wider range of uncertainty about the point estimate than was calculated with fixed-effects models.

Although the random-effects model accommodated variability among studies, the extent of heterogeneity in the trials was examined by 2 methods. The Q statistic of DerSimonian and Laird[23] approximated a χ^2 statistic to test a null hypothesis that all of the studies estimated the same true value. To identify potential sources of heterogeneity, Galbraith radial plots were constructed.[24,25] This method plotted the log OR divided by the standard error against the reciprocal of the standard error. Ninety-five percent of trials should fall within 2 units above or below a line with slope equal to the overall log OR. Trials that exceed the 2-unit boundary deserve further exploration for heterogeneity.

Results

A total of 32 135 patients were included in the analysis (Figure 1). A significant mortality reduction with GP IIb/IIIa

TABLE 2. Acute Coronary Syndrome Trials

Study	n	Year	Load, μg/kg	Infusion, dose/min	Duration, h	Heparin Regimen	Primary End Point	Indication
Eptifibatide								
Schulman et al (Hopkins study)[17]	227	1995	45 90	0.5 μg/kg 1.0 μg/kg	24–72	B+I to PTT 1.5–2.5×control	24-h ischemic episodes	USA
PURSUIT[8]	10948	1996	180 180	1.3 μg/kg 2.0 μg/kg	72	Recommended, details left to physician's discretion	30-d death/MI	USA, NQMI
Tirofiban								
PRISM[7]	3232	1994	18	0.15 μg/kg	48	No heparin vs B+I to PTT 2×control	48-h death/MI/ refractory angina	USA, NQMI
PRISM Plus[18]	1915	1994	0.6 0.4	0.15 μg/kg 0.10 μg/kg	48–60	No heparin vs B+I to PTT 2×control	30-d death/MI/ refractory ischemia	USA, NQMI
Lamifiban								
PARAGON A[19]	2282	1995	300 750	1.0 μg 5.0 μg	72–120	2×2 factorial design; B+I to PTT 60–85 s vs placebo	30-d death/MI	USA, NQMI
Theroux et al[20]	365	1995	150 300 600 750	1 μg 2 μg 4 μg 5 μg	72–120	To PTT 2×control, at physician's discretion	1-mo death/MI	USA, non-ST elevation MI

NQMI indicates non-Q-wave MI; other abbreviations as in Table 1.

inhibitors was observed at the early time point (48 to 96 hours), with an OR of 0.70 (95% CI, 0.51 to 0.96; $P<0.03$) (Figure 2). The combined risk difference of −0.001 (95% CI, −0.0026 to 0.0003) was equivalent to a reduction of 1 death per 1000 patients treated. Trends toward mortality benefit at 30 days and 6 months were not statistically significant. At 30 days, the OR was 0.87 (95% CI, 0.74 to 1.02; $P=0.08$), equivalent to 3 fewer deaths per 1000 patients treated (−0.0032; 95% CI, −0.0063 to −0.0001) (Figure 3). At 6 months, the OR was 0.97 (95% CI, 0.86 to 1.10; $P=0.67$), equivalent to 2 fewer deaths per 1000 patients treated (−0.0015; 95% CI, −0.0059 to 0.0029).

For the combined end point of death or nonfatal MI, there was a highly significant ($P<0.001$) benefit for GP IIb/IIIa inhibitors at every time point. For the early time point (48 to 96 hours), the OR was 0.66 (95% CI, 0.56 to 0.78), equivalent to 17 fewer events per 1000 patients treated (−0.017; 95% CI, −0.023 to −0.011). At 30 days, the OR was 0.76 (95% CI, 0.66 to 0.87), or 20 fewer events per 1000 patients treated (−0.020; 95% CI, −0.029 to −0.012) (Figure 4). At 6 months, the OR was 0.82 (95% CI, 0.74 to 0.91), or 20 fewer events per 1000 patients treated (−0.020; 95% CI, −0.028 to −0.011).

For the composite end point of death, MI, or revascularization, there was a highly significant ($P<0.001$) benefit favoring GP IIb/IIIa inhibitors. For the early time point (48 to 96 hours), the OR was 0.66 (95% CI, 0.58 to 0.75), equivalent to 27 fewer events per 1000 patients treated (−0.027; 95% CI, −0.034 to −0.020). At 30 days, the OR was 0.77 (95% CI, 0.69 to 0.86), or 30 fewer events per 1000 patients treated (−0.030; 95% CI, −0.040 to −0.020) (Figure 5). At 6 months, the OR was 0.89 (95% CI, 0.84 to 0.94), or 23 fewer events per 1000 patients treated (−0.023; 95% CI, −0.033 to −0.012).

Percutaneous Intervention Trials

No significant difference in mortality was seen at any time point. At 48 to 96 hours, the OR was 0.66 (95% CI, 0.34 to 1.31; $P=0.24$). At 30 days, the OR was 0.77 (95% CI, 0.53 to 1.10; $P=0.15$). At 6 months, the OR was 0.90 (95% CI, 0.70 to 1.16; $P=0.41$).

For the combined end point of death or nonfatal MI, there was a highly significant ($P<0.001$) benefit for GP IIb/IIIa inhibitors at all 3 time points. For the early time point (48 to 96 hours), the OR was 0.57 (95% CI, 0.45 to 0.71), equivalent to 27 fewer events per 1000 patients treated (−0.027; 95% CI, −0.037 to −0.017). At 30 days, the OR was 0.64 (95% CI, 0.51 to 0.80), or 27 fewer events per 1000 patients treated (−0.027; 95% CI, −0.040 to −0.014). At 6 months, the OR was 0.76 (95% CI, 0.64 to 0.91), or 23 fewer events per 1000 patients treated (−0.023; 95% CI, −0.037 to −0.009).

For the composite end point of death, MI, or revascularization, there was also a significant benefit favoring GP IIb/IIIa inhibitors. For the early time point (48 to 96 hours), the OR was 0.56 (95% CI, 0.46 to 0.67; $P<0.001$), equivalent to a reduction of 38 events per 1000 patients treated (−0.038; 95% CI, −0.049 to −0.028). At 30 days, the OR was 0.65 (95% CI, 0.54 to 0.79; $P<0.001$), or ~37 fewer events per 1000 patients treated (−0.037; 95% CI, −0.52 to −0.022). At 6 months, the OR was 0.87 (95% CI, 0.80 to 0.95; $P<0.003$), or 28 fewer events per 1000 patients treated (−0.028; 95% CI, −0.045 to −0.012).

Acute Coronary Syndrome Trials

No significant difference in mortality was seen at any time point. At the early time point (48 to 96 hours), the OR was 0.71 (95% CI, 0.50 to 1.01). At 30 days, the OR was 0.90 (95% CI, 0.76 to 1.06). At 6 months, the OR was 1.00 (95% CI, 0.87 to 1.15).
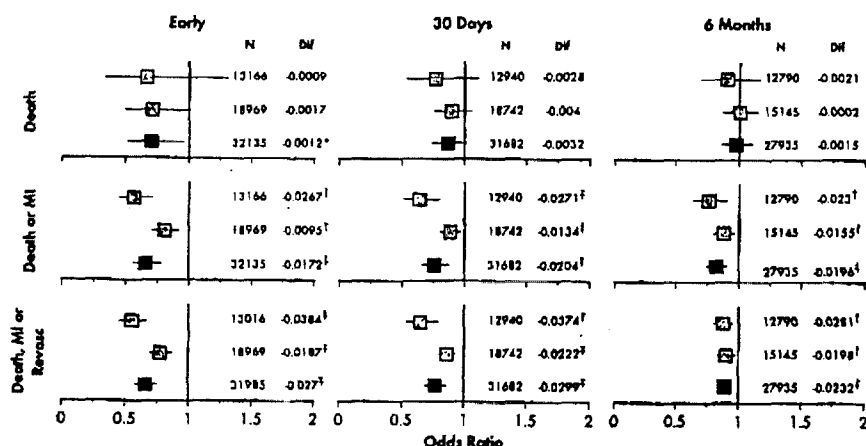
Figure 1. ORs and 95% CIs for risk of death, death or MI, and death, MI, or revascularization (Revasc) 48 to 96 hours, 30 days, and 6 months after randomization to a GP IIb/IIIa inhibitor (vs placebo). ORs are given for combined percutaneous intervention trials (▨), combined non–ST-segment elevation acute coronary syndromes trials (▩), and all collected trials (■). N indicates sample size; Dif, risk difference. *$P<0.05$; †$P<0.01$; ‡$P<0.001$.

For the combined end point of death or nonfatal MI, there was a significant ($P<0.01$) benefit for GP IIb/IIIa inhibitors early and at 30 days. At the early time point (48 to 96 hours), the OR was 0.81 (95% CI, 0.71 to 0.92), equivalent to a reduction of 10 events per 1000 patients treated (−0.010; 95% CI, −0.015 to −0.004). At 30 days, the OR was 0.88 (95% CI, 0.81 to 0.97), or 13 fewer events per 1000 patients treated (−0.013; 95% CI, −0.023 to −0.004). At 6 months, the OR was 0.88 (95% CI, 0.79 to 0.97), equal to 16 fewer events per 1000 patients treated (−0.016; 95% CI, −0.027 to −0.004).

For the composite end point of death, MI, or revascularization, there was a highly significant benefit favoring GP IIb/IIIa inhibitors. For the early time point (48 to 96 hours), the OR was 0.77 (95% CI, 0.69 to 0.86; $P<0.001$), equivalent to 19 fewer events per 1000 patients treated (−0.019; 95% CI, −0.027 to −0.011). At 30 days, the OR was 0.86 (95% CI, 0.80 to 0.93; $P<0.001$), or 22 fewer events per 1000 patients treated (−0.022; 95% CI, −0.034 to −0.010). At 6 months, the OR was 0.90 (95% CI, 0.83 to 0.97; $P<0.01$), or 20 fewer events per 1000 patients treated (−0.020; 95% CI, −0.036 to −0.004).

Heterogeneity Analyses

For percutaneous intervention trials, the Q statistic revealed significant heterogeneity for the death/MI end point at 30 days and 6 months and for death/MI/revascularization at 48 to 96 hours and 30 days. No significant heterogeneity was detected in the acute coronary syndrome trials. The test of heterogeneity for the entire trial collection reflected the heterogeneity present within the percutaneous intervention subgroup.

Galbraith plots (Figure 6) identified the EPILOG trial's particularly pronounced effect in favor of GP IIb/IIIa blockade. This finding corresponds to the quantitative results. Q statistics calculated without the EPILOG trial are consistent with homogeneity for all end points except early (48 to 96 hours) death/MI/revascularization. Thus, EPILOG contributed substantially to the statistical heterogeneity of the collected trials.

Discussion

This new therapeutic class promises a substantial benefit when applied to clinical practice. Patients undergoing percutaneous coronary intervention or presenting with an acute
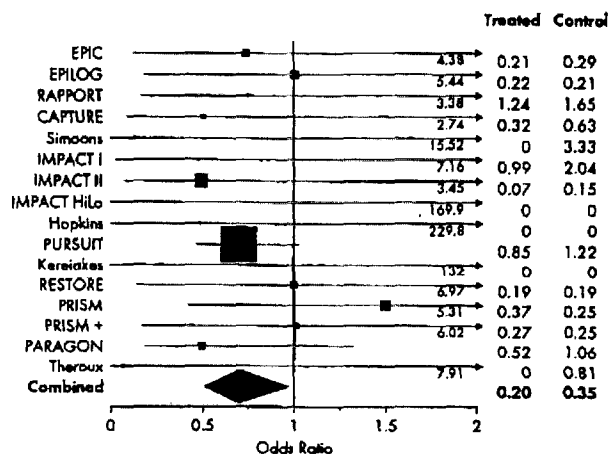

Figure 2. ORs and 95% CIs for risk of death between 48 and 96 hours after randomization to a GP IIb/IIIa inhibitor (vs placebo). Event rates are listed for treated and control arms in each study and for combined trials.
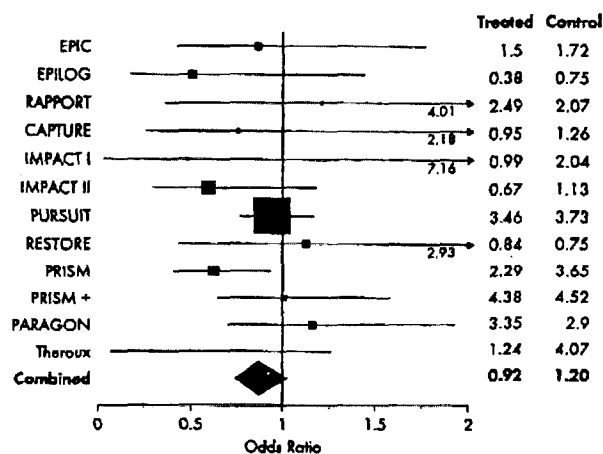

Figure 3. ORs and 95% CIs for risk of death 30 days after randomization to a GP IIb/IIIa inhibitor vs placebo. Event rates are listed for treated and control arms in each study and for combined trials.
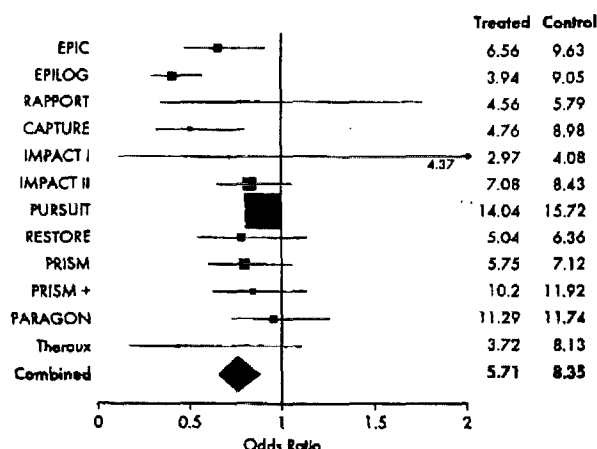
Figure 4. ORs and 95% CIs for risk of death or MI 30 days after randomization to a GP IIb/IIIa inhibitor vs placebo. Event rates are listed for treated and control arms in each study and for combined trials.

coronary syndrome can expect a significant reduction in critical clinical events, including nonfatal MI and the need for repeat procedures. Much of the benefit occurs early in the patient's clinical course and is maintained at 6 months.

The effect of GP IIb/IIIa inhibitors on mortality is small compared with the number of patients studied. One might infer that no mortality benefit exists, simply because the 6-month result is not statistically significant. Another explanation recognizes that the absolute benefit (lives saved per 1000 patients treated) remains constant between the early phase and 6 months. In the early phase (during drug infusion), the 35% relative mortality reduction and paucity of deaths overall make this difference borderline statistically significant. Afterward, the numbers of additional deaths in the treatment and control groups are similar, suggesting no further effect on mortality after the infusion ends. Because deaths accumulate equally in both groups over time, the relative effect (ORs and P value) declines and becomes nonsignificant. In addition, although the point estimates
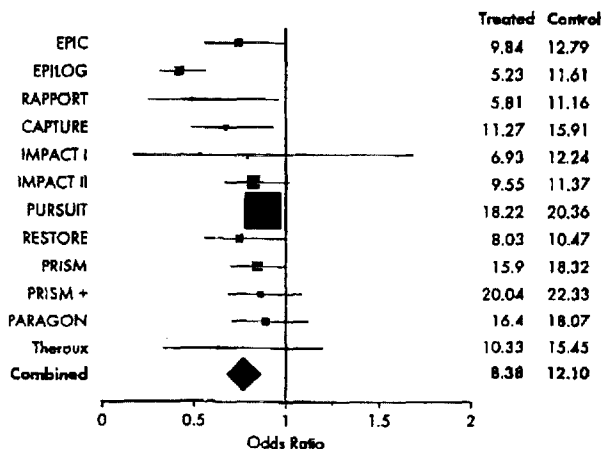

Figure 5. ORs and 95% CIs for risk of death, MI, or revascularization 30 days after randomization to a GP IIb/IIIa inhibitor vs placebo. Event rates are listed for treated and control arms in each study and for combined trials.

remain relatively constant, the CIs widen because fewer patients had 6-month data than had 48- to 96-hour data. Last, the 30-day mortality rate was only 2.7% for the combined control arms. Proof of a mortality difference given this event rate requires either a monumental treatment effect or an enormous sample size (145 618 patients to detect a 10% relative reduction with 90% power, or 21 872 patients for a 25% reduction.) The probability of a detrimental effect on mortality is <3% for GP IIb/IIIa inhibitors given intravenously for 1 to 4 days. Long-term dosing of oral formulations may extend this effect to a larger, durable mortality benefit.

Definitions of nonfatal MI and reinfarction varied among trials, with different enzyme, ECG, and clinical criteria. A majority of the trials used adjudication committees in addition to (often complex) formal descriptive rules. The disparity among investigators and sponsors is a limitation of the trial designs in this area. Although a consensus end-point definition is highly desirable for future trials, there is at present no feasible way to reconstruct a uniform definition for previous studies. Despite this limitation, any MI, however defined, constitutes an undesirable event for patients, and we have reported results consistent with primary-end-point definitions.

Ten of the 16 trials used a composite of death, MI, or revascularization as the primary end point. A larger reduction in relative odds exists for combined death/MI events than for composite death/MI/revascularization events. Applied to 1000 patients similar to the overview population, GP IIb/IIIa blockade would prevent 20 of 91 deaths or nonfatal MIs in the first 30 days, a 22% relative reduction. Under the same conditions, the agents would prevent 30 of 169 deaths, MIs, or revascularization procedures (a 17% reduction). From a treatment policy perspective, the triple end point better reflects the anticipated benefit to clinical practice.

Efforts to accumulate all available information inevitably increase the potential for heterogeneity in pooled data. Formal tests for heterogeneity have low power. Thus, statistical failure to reject the null hypothesis of homogeneity does not imply equality[26] but rather a lack of unacceptable heterogeneity. In this overview, the methods used to calculate the combined ORs accommodate heterogeneity.[21,27] The overview combines studies of 3 agents with those of abciximab, which has a longer duration of action and cross-reactivity with the $\alpha_v\beta_3$ receptor.[28] As previously mentioned, patient characteristics, therapeutic regimens, end-point definitions, and adjunctive drugs (heparin and aspirin) were nonuniform across trials. The EPILOG trial contributed strongly to the statistical heterogeneity of the collected trials. The pronounced power of EPILOG may stem from its early termination,[29,30] the patient population, the dosing regimen, or inherent drug effects.

Whether differences in clinical benefit exist among the different compounds is speculative. The variability present among trials precludes indirect comparisons of individual agents. These differences can produce disparity among trials included in meta-analyses[31] and cause discrepancies between meta-analyses and subsequent large, controlled trials. For example, Fox[32] attempted indirect comparisons between anistreplase and alteplase using a fixed-effects model. The ISIS-3
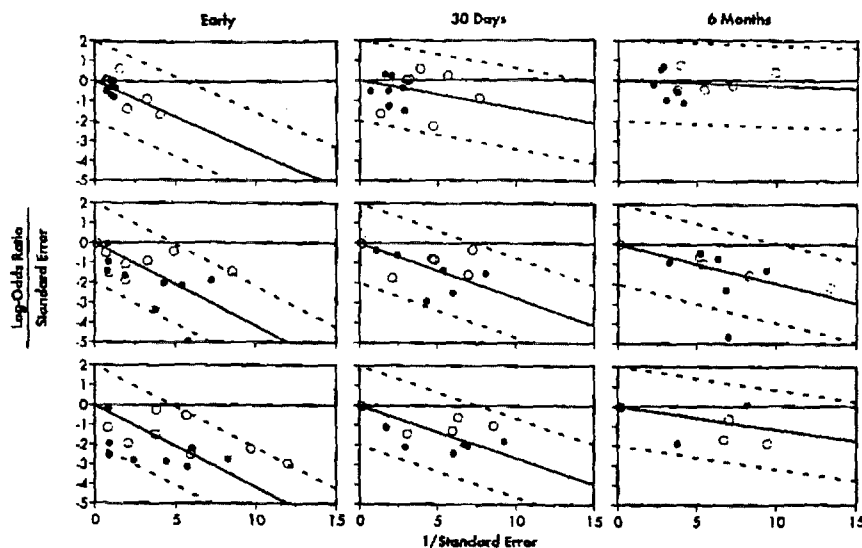
Figure 6. Galbraith plots of heterogeneity for percutaneous intervention trials (●) and acute coronary syndrome trials (O) for death (top row), death or MI (middle row), and death, MI, or revascularization (bottom row) 48 to 96 hours, 30 days, and 6 months after randomization to a GP IIb/IIIa inhibitor or placebo. In a statistically homogeneous sample, 95% of trials should fall within 2 units (dashed lines) of overall OR (solid diagonal line).

randomized trial[33] later showed no significant difference between the 2 agents. Although practice guidelines should be influenced most by large randomized trials, properly conducted systematic overviews of large trials can describe overall benefit and summarize past experience better than individual studies examined separately.

The general mechanism of benefit is undoubtedly the inhibition of platelet aggregation, a critical component of thrombotic coronary occlusion. At 30 days, the trials of percutaneous intervention had a significantly larger relative reduction in combined death and MI than the acute coronary syndromes trials (95% CI, 0.51 to 0.80 versus 0.81 to 0.97, respectively), although the 95% CIs overlapped at the other 2 time points. These agents may perform better during angioplasty, when delivered at a time of arterial trauma and platelet aggregation. This difference also may represent a reduction in postprocedure myocardial enzyme elevation. The lesser benefit for acute coronary syndromes may reflect the delay between the initial intimal insult and institution of therapy. The optimal degree and duration of GP IIb/IIIa inhibition remain to be established for each indication.

The GP IIb/IIIa inhibitors clearly show a consistent, substantial, and durable benefit as a therapeutic class. Future randomized, comparative clinical trials will undoubtedly refine these results and identify optimal applications for specific agents. The completion of definitive outcome studies before regulatory approval should speed assimilation of these agents into clinical practice and transformation of these promising results into new standards of care.

Acknowledgments

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